ORIGINAL ARTICLE EPIDEMIOLOGY AND GENETICS

Does allergic rhinitis exist in infancy? Findings from the PARIS birth cohort

M. Herr[1], B. Clarisse[1], L. Nikasinovic[1], C. Foucault[2], A.-M. Le Marec[3], J.-P. Giordanella[2], J. Just[1,4] & I. Momas[1,3]

[1]Université Paris Descartes, EA 4064, Laboratoire Santé Publique et Environnement, Paris; [2]Centre d'Examens de Santé de l'Enfant Amelot, CPAM de Paris; [3]Cellule Cohorte de la Direction de l'Action Sociale, de l'Enfance et de la, Santé de la Mairie de Paris; [4]Centre de l'Asthme et des Allergies, Groupe Hospitalier Trousseau-La Roche Guyon, Assistance Publique – Hôpitaux de Paris, Paris, France

To cite this article: Herr M, Clarisse B, Nikasinovic L, Foucault C, Le Marec A-M, Giordanella J-P, Just J, Momas I. Does allergic rhinitis exist in infancy? Findings from the PARIS birth cohort. *Allergy* 2011; **66**: 214–221.

Keywords
eosinophils; epidemiology; IgE; paediatrics; rhinitis.

Correspondence
Prof. Isabelle Momas, Laboratoire Santé Publique et Environnement, EA 4064 – Faculté des Sciences Pharmaceutiques et Biologiques, 4 avenue de l'Observatoire, 75006 Paris, France.
Tel.: 33 1-53-73-97-26
Fax: 33 1-43-25-38-76
E-mail: isabelle.momas@parisdescartes.fr

Accepted for publication 10 July 2010

DOI:10.1111/j.1398-9995.2010.02467.x

Edited by: Wytske Fokkens

Abstract

Background: Early onset of allergic rhinitis (AR) is poorly described, and rhinitis symptoms are often attributed to infections. This study analyses the relations between AR-like symptoms and atopy in infancy in the PARIS (Pollution and Asthma Risk: an Infant Study) birth cohort.

Methods: Data on AR-like symptoms (runny nose, blocked nose, sneezing apart from a cold) were collected using a standardized questionnaire administered during the health examination at age 18 months included in the follow-up of the PARIS birth cohort. Parental history of allergy and children's atopy blood markers (blood eosinophilia ≥470 eosinophils/mm^3, total immunoglobulin E ≥45 U/ml and presence of allergen-specific IgE) were assessed. Associations were studied using multivariate logistic regression models adjusted for potential confounders.

Results: Prevalence of AR-like symptoms in the past year was 9.1% of the 1850 toddlers of the study cohort. AR-like symptoms and dry cough apart from a cold were frequent comorbid conditions. Parental history of AR in both parents increased the risk of suffering from AR-like symptoms with an OR 2.09 (P = 0.036). Significant associations were found with the presence of concurrent biological markers of atopy, especially blood eosinophilia and sensitization to house dust mite (OR 1.54, P = 0.046 and OR 2.91, P = 0.042) whereas there was no relation with sensitization to food.

Conclusions: These results support the hypothesis that AR could begin as early as 18 months of life. Suspicion of AR should be reinforced in infants with parental history of AR or biological evidence of atopy, particularly blood eosinophilia and sensitization to inhalant allergens.

Despite the recognition that allergic rhinitis (AR) affects an increasing proportion of preschool children, there is a paucity of data regarding epidemiology of AR in infancy (1). This is partly because of the difficulty of recognizing symptoms related to allergy and symptoms related to infections. Because they often share similar clinical symptoms (sneezing, nasal congestion and nasal discharge), AR and nonallergic rhinitis are difficult to differentiate (1).

The relation of rhinitis symptoms with atopy has been shown in children aged 4 years (2, 3) but the existence of such a relation is still discussed in infancy. Nevertheless, identification of an early onset of AR is important because AR has been shown to be associated with impairments in quality of life, sleep disorders, learning problems and medical complications affecting ears and sinus (4). In addition, recent findings from Chawes et al. (5) suggested the irreversible nature of nasal airways obstruction caused by AR in childhood. Their results indicated that AR could lead to chronic inflammation and structural remodelling of the nasal mucosa in children as young as 6 years. Apart from this, there is epidemiological evidence of a relation between AR and asthma (6), AR being a risk factor for the development of asthma in childhood (7).

This study is part of the PARIS (Pollution and Asthma Risk: an Infant Study) birth cohort, a population-based study

implemented in 2003 dealing with respiratory and allergic disorders in early childhood. The aim of this study is (i) to describe the prevalence of symptoms suggestive of AR, so-called AR-like symptoms and (ii) to study the relations between AR-like symptoms and factors related to atopy, predisposition to atopy represented by parental history of allergy in the one hand, and current atopy assessed through biological markers in the child on the other hand.

Materials and methods

Population and ethics

This study analyses data gathered during a health examination given to every child aged 18 months included in the PARIS birth cohort, a population-based cohort composed of healthy children recruited at birth in five Parisian maternity hospitals according to both medical and socio-demographic criteria (8). Enrolled children were singleton full-term newborns, with a birth weight ≥2500 g and an uncomplicated birth and neonatal period. The health examination was proposed to the 3436 children still followed up at 1 year of age in the PARIS birth cohort (82.3% of the children initially included). This was a free-of-charge health examination that took place in the Paris Health Centre of the National French Health Insurance System. It included a medical examination together with a standardized questionnaire administered by a paediatrician. A blood sample was taken for each child and analysed for different biological markers of atopy. The parents of all children involved in the study gave their informed consent, and the research protocol was approved by the National Ethics Committee (permissions no. 031153 and 051289).

Health outcomes

Parents were given a standardized questionnaire by a paediatrician in search of the occurrence of AR-like symptoms (nasal congestion or nasal discharge, sneezing) and other respiratory and allergic outcomes, particularly wheezing, dry cough apart from a cold and eczema. A child was considered as presenting AR-like symptoms if parents answered 'yes' to the question 'In the past 12 months, did your child have a problem with sneezing, or a runny, or a blocked nose when she/he did not have a cold or the flu?'. Moreover, parents were asked whether these symptoms were combined with watery eyes, how many months they last and whether they disturb daily activities of the child. Wheezing was defined as whistling in the chest in the last 12 months, no matter whether it occurred during an infection or not, while dry cough was defined as a dry cough specifically occurring apart from a cold or the flu. The recurrence of episodes for wheezing and dry cough was regarded as more than three episodes in the past year according to the International Study of Asthma and Allergies in Childhood (ISAAC). Eczema was defined as a red and itchy skin rash that had been coming and going for at least 6 months. Parents were also asked whether a doctor had ever diagnosed their child with an allergy.

Biological markers of atopy

Full blood count was determined, and blood eosinophilia was measured by using flow cytometry (Beckmann Coulter, Miami, FL, USA). Blood eosinophilia is expressed as the absolute value per cubic millimetre (eosinophils/mm^3). Total immunoglobulins E (IgE) were measured by using ImmunoCAP™ (Phadia, Uppsala, Sweden) and are expressed in units per millilitre (U/ml). Serum IgE antibodies to inhalant and food allergens were analysed with ImmunoCAP™ Phadiatop® and Trophatop® fx26, fx27 and fx28 (Phadia). Sensitization to inhalant allergens was defined as a positive ImmunoCAP™ Phadiatop® [a mixture of house dust mite (including *Dermatophagoides pteronyssinus*), pets (including cat), grass pollens, weed pollens, tree pollens and mould (including *Alternaria tenuis*)]. A positive result led to the measurement of specific IgE directed towards four inhalant allergens (*D. pteronyssinus*, *A. tenuis*, cat dander, grass pollen). As to sensitization to food allergens, it was defined as a positive test among ImmunoCAP™ Trophatop® fx26 (egg white, cow's milk, peanut, mustard), Trophatop® fx27 (fish, wheat, soy, hazelnut) and Trophatop® fx28 (sesame, shrimp, beef, kiwi). If one of the tests was positive, measurement of specific IgE directed towards the respective food allergens was taken. The detection limit for ImmunoCAP™ Phadiatop® and Trophatop® fx26, fx27, fx28 as well as measurements of specific IgE antibodies was set at 0.35 U/ml.

Other factors

Data regarding potential risk factors for rhinitis in the children were collected using questionnaires at 1, 3, 6, 9, 12 and 18 months of age dealing with household environment and lifestyle. Parental history of allergy was assessed, focusing on whether they had ever experienced AR, asthma and/or eczema. Socio-economic status (SES) was determined according to the highest level of occupation among the two parents. Occupations were divided into three categories being low (low-level white-collar workers, blue-collar workers, unemployed and students), intermediate (intermediate white-collar workers, craftsmen and shopkeepers) and high (high-level white-collar workers). Duration of breastfeeding was recorded. Finally, parents were asked about prenatal and postnatal exposure to tobacco smoke, prenatal exposure being characterized by active smoking and/or passive smoking at home or at work during pregnancy while postnatal tobacco smoke exposure was defined as a positive answer to the question: 'Is somebody smoking at home every day?'

Statistical analysis

Analyses were performed by using STATA® software, version 9.1 (StataCorp, College Station, TX, USA). Chi-square tests were used to compare the prevalence of comorbidity and factors related to atopy between infants with AR-like symptoms and those without AR-like symptoms. The values of total IgE and blood eosinophils were log-transformed and the comparison of values between infants according to

AR-like symptoms used a Student's *t*-test. In addition to their analysis as continuous variables, levels of total IgE and blood eosinophils were studied as binary outcomes by using thresholds defining elevated levels. Blood eosinophilia was defined as a concentration of 470 eosinophils/mm^3 or greater and elevated total IgE as a concentration of 45 U/ml or greater. These critical thresholds of common biological markers of atopy were previously determined in a population of comparable age (toddlers aged < 30 months) with regard to their association with the persistence of wheezing in childhood (9). Potential confounding effects were researched by assessing the relations between potential confounders and both AR-like symptoms and factors related to atopy. Unconditional multivariate logistic regression was used to study the relations between the occurrence of AR-like symptoms and factors related to atopy. Results were adjusted on factors known as potential confounders for the development of atopy in childhood (gender, level of parental SES, siblings, duration of maternal breastfeeding, prenatal and postnatal exposure to tobacco smoke). Modifying effects were assessed by testing interactions between the variables introduced in the multivariate regression models. Results are presented with adjusted odds ratios (OR) and 95% confidence intervals (CI).

Results

Among the 2012 toddlers who came to the health examination, the analysis was carried out on the 1850 who had both information on the prevalence of AR-like symptoms and measurements of at least one biological marker (blood eosinophilia, total and allergen-specific IgE). Table 1 shows the comparison between children participating in the analysis and the other 2327 children included in the original PARIS cohort but not participating. There was no difference with regard to gender, number of siblings, parental history of allergy and parental smoking. Differences were found in maternal age and parental SES level, with a higher proportion of upper-level SES in the families participating compared to those not participating. Moreover, focusing on children the health examination was proposed to (n = 3436), i.e. children still followed up in the cohort at 1 year of age, the comparison between participants and nonparticipants did not reveal any difference with regard to parental smoking during the first year of life, maternal breastfeeding and incidence of respiratory and allergic disorders (wheezing, eczema and AR-like symptoms) at 1 year of age (data not shown).

The mean age of the children of our study sample was 19 months ± 2, and the sex ratio was 1. Data regarding the prevalence of respiratory and allergic outcomes are given in Table 2. AR-like symptoms were reported in 169 children in the past 12 months, which corresponds to a prevalence of 9.1% (95% CI 7.8–10.4%). There was no difference between boys and girls (9.4% *vs* 8.9%, P = 0.687). The most reported symptom was runny nose, in 117 children (69.2%), followed by sneezing in 54 children (32.0%) and blocked nose in 35 children (20.7%). Watery eyes were combined with nasal symptoms in 40 cases (23.7%). The mean duration of the symptoms over the year was estimated at

Table 1 Population characteristics of infants followed up in the PARIS birth cohort according to their participation in the analysis at 18 months of age

	*n** (%)		
	Analysed subcohort (*n* = 1850)	Children of the original birth cohort not included in the analysis (*n* = 2327)	*P*
Gender			
Male	925 (50.0)	1207 (51.9)	0.230
Female	925 (50.0)	1120 (48.1)	
Siblings			
0	1059 (57.2)	1288 (55.4)	0.101
1	614 (33.2)	771 (33.1)	
≥2	177 (9.6)	268 (11.5)	
Parental history of allergy			
Asthma	345 (18.7)	439 (18.9)	0.858
AR	657 (35.5)	772 (33.2)	0.114
Eczema	308 (16.7)	418 (18.0)	0.265
Parental SES			
High	1231 (66.5)	1299 (55.8)	<0.001
Intermediate	476 (25.7)	706 (30.3)	
Low	143 (7.7)	322 (13.8)	
Maternal age in years (mean ± SD)	32.5 ± 4.0	32.1 ± 4.3	0.001
Prenatal exposure to tobacco smoke	551 (29.8)	753 (32.4)	0.100
Parental smoking	385 (21.1)	482 (23.1)	0.118

AR, allergic rhinitis; SES, socio-economic status.
*Number of infants may vary because of missing information.

Table 2 Prevalence of respiratory and allergic outcomes depending on the occurrence of allergic rhinitis (AR)-like symptoms in infants from the PARIS birth cohort participating in the health examination at 18 months of age

	*n** (%)			
Respiratory and allergic outcomes	Total (*n* = 1850)	AR-like symptoms (*n* = 169)	No AR-like symptoms (*n* = 1681)	*P*
Wheezing	522 (28.3)	54 (32.0)	468 (27.9)	0.262
Occasional†	474 (25.7)	48 (28.4)	426 (25.4)	0.390
Recurrent‡	48 (2.6)	6 (3.6)	42 (2.5)	0.413
Dry cough apart from a cold	164 (8.9)	37 (21.9)	127 (7.6)	<0.001
Occasional†	129 (7.0)	27 (16.0)	102 (6.1)	<0.001
Recurrent‡	35 (1.9)	10 (5.9)	25 (1.5)	<0.001
Eczema	280 (15.2)	31 (18.6)	249 (14.9)	0.204
Doctor-told allergy	144 (8.0)	31 (18.7)	113 (6.9)	<0.001

*Number of infants may vary because of missing information.
†1–3 episode(s) a year.
‡>3 episodes a year.

3.9 months ± 3. Symptoms were considered as disturbing the daily activity of the child in 30 cases (17.8%). Infants with AR-like symptoms did not have increased prevalence of wheezing and eczema compared to those without, whereas they were significantly more likely to report dry cough apart from a cold and doctor-told allergy (Table 2).

Population characteristics such as gender, SES level, number of siblings, parental smoking and duration of maternal exclusive breastfeeding did not differ between infants suffering from AR-like symptoms and the others (Table 3). On the contrary, a parental history of AR was found to be specifically related to the occurrence of AR-like symptoms whereas parental history of asthma and eczema was not.

Results from the measurements of different biological markers of atopy are shown in Table 3. Allergen-specific sensitization was found in 294 children (16.3%). Sensitization to food allergen was much more common than sensitization to inhalant allergens and mainly concerned cow milk (n = 137; prevalence = 7.7%), egg white (n = 120; prevalence = 6.8%), hazelnut (n = 41; prevalence = 2.3%) and peanut (n = 34; prevalence = 1.9%). As far as sensitization to inhalant allergens is concerned, house dust mite (*D. pteronyssinus*) was the most common inhalant allergens (n = 22; prevalence = 1.2%) followed by cat (n = 19; prevalence = 1.1%), grass pollen (n = 3; prevalence = 0.2%) and mould (*A. tenuis*) (n = 1; prevalence = 0.1%). Infants suffering

Table 3 Distribution of the different variables of interest depending on the occurrence of allergic rhinitis (AR)-like symptoms in infants from the PARIS birth cohort participating in the health examination at 18 months of age

	*n** (%)			
	Total (n = 1850)	AR-like symptoms (n = 169)	No AR-like symptoms (n = 1681)	*P*
Male gender	925 (50.0)	87 (51.5)	838 (49.6)	0.687
SES level				
High	1231 (66.5)	109 (64.5)	1122 (66.8)	0.329
Intermediate	476 (25.7)	42 (24.9)	434 (25.8)	
Low	143 (7.7)	18 (10.7)	125 (7.4)	
Siblings				
0	1059 (57.2)	92 (54.4)	967 (57.5)	0.646
1	614 (33.2)	58 (34.3)	556 (33.1)	
≥2	177 (9.6)	19 (11.2)	158 (9.4)	
Prenatal exposure to tobacco smoke	551 (29.8)	57 (33.7)	494 (29.4)	0.240
Postnatal exposure to tobacco smoke	550 (29.9)	48 (28.7)	502 (30.0)	0.741
Exclusive maternal breastfeeding				
No	313 (16.9)	24 (14.2)	289 (17.2)	0.609
<3 months	1011 (54.7)	96 (56.8)	915 (54.4)	
≥3 months	526 (28.4)	49 (29.9)	477 (28.4)	
Parental history of allergy				
Asthma	345 (18.7)	37 (21.9)	308 (18.3)	0.257
AR	657 (35.5)	74 (43.8)	583 (34.7)	0.019
Eczema	308 (16.7)	29 (17.2)	279 (16.6)	0.854
Biological markers of atopy				
Eosinophilia (≥470 eosinophils/mm^3)	233 (12.9)	31 (18.8)	202 (12.3)	0.018
Elevated total IgE (≥45 U/ml)	396 (21.9)	46 (27.5)	350 (21.3)	0.065
Allergen-specific sensitization	294 (16.3)	33 (19.9)	261 (16.0)	0.192
Food allergens	269 (15.0)	27 (16.4)	242 (14.8)	0.601
Food allergens only	240 (13.3)	24 (14.5)	216 (13.2)	0.650
Inhalant allergens	52 (2.9)	9 (5.5)	43 (2.7)	0.040
Dermatophagoides pteronyssinus	22 (1.2)	5 (3.1)	17 (1.1)	0.026
Inhalant allergens only	25 (1.4)	6 (3.6)	18 (1.1)	0.007
Both food and inhalant allergens	27 (1.5)	3 (1.8)	24 (1.5)	0.731
Biological markers of atopy†				
1	419 (24.1)	43 (26.9)	376 (23.8)	0.380
≥2	113 (6.1)	19 (11.9)	94 (5.9)	0.004

*Number of infants may vary because of missing information.

†Considering eosinophilia ≥470 eosinophils/mm^3, total IgE ≥ 45 U/ml and sensitization to inhalant allergens only.

from AR-like symptoms did not differ from infants not suffering from these symptoms with regard to their level of total IgE (geometric mean + 95% CI: 18 [14–22] *vs* 15 [14–16], $P = 0.098$) and blood eosinophils (geometric mean + 95% CI: 220 [194–250] *vs* 214 [206–222], $P = 0.650$). Nevertheless, the use of critical thresholds for these variables enabled to shed light on differences between groups defined according to the occurrence of AR-like symptoms in the past 12 months and infants with AR-like symptoms were more likely to have blood eosinophilia and also tended to have an elevated level of total IgE. Furthermore, while there was no relation with sensitization to food allergens, infants with AR-like symptoms had an increased rate of sensitization to inhalant allergens, particularly house dust mite, compared to children without AR-like symptoms.

The relation between the occurrence of AR-like symptoms and a parental history of AR persisted in multivariate analysis when both parents reported AR (Table 4). As for biological markers of atopy, blood eosinophilia accounted for an increase >50% in the risk of AR and sensitization to inhalant allergens more than doubled the risk of occurrence of AR-like symptoms. Sensitization to house dust mite was a strong predictor of AR-like symptoms with an OR of almost 3. The addition of two or more biological markers of atopy was related to a significantly higher risk of suffering from AR-like symptoms compared to markers taken separately.

Table 4 Multivariate analysis of the relations between the occurrence of allergic rhinitis (AR)-like symptoms and factors related to atopy in infants from the PARIS birth cohort participating in the health examination at 18 months of age ($N = 1850$)

	Adjusted OR	95% CI	*P*
*Parental history of AR**			
Model 1			
No	1		
Father	1.19	0.80–1.76	0.387
Mother	1.54	1.06–2.24	0.025
Model 2			
No	1		
1 parent	1.28	0.90–1.82	0.166
Both parents	2.09	1.05–4.16	0.036
Biological markers of atopy†			
Model 3			
Eosinophilia (≥470 eosinophils/mm^3)			
No	1		
Yes	1.54	1.01–2.37	0.046
Model 4			
Elevated total IgE (≥45 U/ml)			
No	1		
Yes	1.37	0.94–1.99	0.097
Model 5			
Food allergen sensitization			
No	1		
Yes	1.13	0.73–1.76	0.573
Model 6			
Inhalant allergen sensitization			
No	1		
Yes	2.21	1.05–4.68	0.038
Model 7			
Sensitization to *Dermatophagoides pteronyssinus*			
No	1		
Yes	2.91	1.04–8.16	0.042
Model 8			
Biological markers of atopy‡			
0	1		
1	1.29	0.88–1.89	0.198
≥2	2.16	1.24–3.77	0.007

SES, socio-economic status.
*OR were adjusted for gender, level of parental SES, siblings, duration of exclusive maternal breastfeeding, prenatal and postnatal exposure to tobacco smoke (none of them was significant) and biological markers of atopy (number of biological markers of atopy).
†OR were adjusted for gender, level of parental SES, siblings, duration of exclusive maternal breastfeeding, prenatal and postnatal exposure to tobacco smoke (none of them was significant) and parental history of AR (number of parents with AR).
‡Considering eosinophilia ≥470 eosinophils/mm^3, total IgE ≥ 45 U/ml and sensitization to inhalant allergens only.

Discussion

Main findings

This study reveals that 9.1% of the children experienced AR-like symptoms in the last year by age 18 months. Significant associations were found between the occurrence of these symptoms and an atopic status. Children with a history of AR in both parents or biological evidence of atopy were more likely to have AR-like symptoms than those without. Our results from a large sample of infants aged 18 months confirm the findings of epidemiological studies which suggest that AR could begin as soon as the first year of life (10–12).

Prevalence of AR-like symptoms

Birth cohorts report prevalence of AR before age two varying from 3% to 29% (13–19). This variability in AR data is because of the lack of universally accepted criteria for describing AR in infancy. As a result, different definitions of AR are used and the more limiting the definition, the lower the prevalence. Studies using wide definition such as 'runny nose apart from colds' (13) report the higher prevalence, between 7% and 29% (13–16) whereas studies using more stringent definitions, such as a combination of symptoms (at least two symptoms among runny nose, blocked nose, sneezing and itching/watering eyes) (17, 18) or a medical diagnosis of AR (19), report a prevalence of about 3–4%. In accordance with other epidemiological studies, the present study considered the absence of infection as an important diagnostic criterion. As for clinical outcomes, AR-like symptoms were not highly stringently defined because the definition we used considered the occurrence of at least one of the standard manifestations of AR (nasal congestion, nasal discharge

and sneezing). The figure of 9.1% found in this work is consistent with data from the literature given the definition used.

AR-like symptoms and comorbidity

This study shows that dry cough apart from a cold and AR-like symptoms were frequent comorbid conditions, supporting previous findings from the PARIS birth cohort suggesting the existence of a particular phenotype of infants associating dry cough apart from a cold and nasal symptoms (20). No relation was found with the occurrence of wheezing in the past year, contrary to other epidemiological studies (13, 21) which have succeeded in demonstrating that AR and asthma are strongly related with each other in children. Nevertheless, these studies examined older children (5–6 years old) while this study deals with infants and, consequently, faces the complex aetiology of wheezing in infancy, wheezing being mainly related to exposure to virus at this age rather than to atopy (13). According to the 'allergic march hypothesis', skin symptoms are generally the first atopic symptoms to occur in life, followed later by AR and asthma. However, we found no relation between the occurrence of AR-like symptoms and eczema. According to this result, AR could be the emerging signal of the presence of the atopic status independently from skin symptoms.

AR-like symptoms and factors related to atopy

Our results indicate a strong genetic component in the development of AR-like symptoms in infancy, as evidenced by the twofold increase in risk associated with a history of AR in both parents, even if it is possible that one parent might not know the complete history of allergy of the other parent and no assessment of parental atopy was made. Interestingly, such a relation was not found with parental history of asthma or eczema. The hypothesis of inherited atopic phenotype predisposition is supported by the results of the Avon Longitudinal Study of Parents and Children (ALSPAC): a similar relation with eczema was observed, parental history of eczema being a better marker than parental asthma/hay fever in predisposing childhood eczema (22). However, the specificity of the association found in this study could also reflect a labelling phenomenon, i.e. parents with AR are more likely to notice rhinitis symptoms in their children.

The association we found between the occurrence of AR-like symptoms and blood eosinophilia suggests a link between rhinitis and atopy in infancy, because blood eosinophilia has been suggested to be an early sign of allergic inflammation (9). The relation between the occurrence of AR-like symptoms and an elevated level of total IgE was of borderline significance. Nevertheless, the direction of the relation was as expected and the use of a cut point and the resulting small sample in the high group may be the issue, as well as the wide variability of IgE levels in infancy (23, 24). Indeed, levels of total IgE in early life have been shown to be poorly correlated to levels observed in childhood (23) and to be influenced by exposures to environmental pollutants (25) or virus (26). One of the major findings of this study is the significant association found between the prevalence of AR-like symptoms and sensitization to inhalant allergens, especially house dust mite allergens, whereas there was no association with sensitization to food allergens. The greater role of sensitization to inhalant allergens compared to food allergens in the occurrence of AR was actually shown in older children (2). Nevertheless, we found that AR-like symptoms were particularly associated with sensitization to house dust mite allergens rather than with sensitization to pollens as observed in older children (2). This difference seems coherent as house dust mite allergens have been identified as the main source of sensitization to inhalant allergens in early life (2, 26). Furthermore, sensitization to pollens is supposed to require at least two seasons of exposure (27). In addition to the separate analysis of biological markers, the analysis of the number of markers has shown that infants were particularly at risk of suffering from AR-like symptoms if they had two or more biological evidences of atopy (excluding sensitization to food). This last analysis supports the findings of other studies which have suggested that identification of atopy in infants is more reliable when using a combination of different evidences (28, 29).

Strength and limitations of the study

The strength of this study is that it objectively measures atopy in a large sample of infants under 2 years of age: there are only a few birth cohorts for which biological markers of atopy are available within the first 18 months of life (30, 31). At about 18 months of age, the child's immune system is building up and the biological expression of an atopic predisposition varies depending on the maturity of the immune system. To take this variability into account, it appeared relevant to study biological evidence of atopy according to different standards including blood eosinophilia, total IgE and allergen-specific sensitization. The choice of the thresholds to define elevated levels of total IgE and eosinophilia was supported by their consistency with those found in other studies, ranging between 30 and 51 U/ml for total IgE (29, 32, 33) and between 400 and 600 eosinophils/mm^3 for eosinophilia (34, 35). From a methodological standpoint, we consider that the involvement of a paediatrician in the administration of the questionnaire improves the quality of the data. The four paediatricians participating in the study were specifically trained to administer the questionnaire to guarantee the homogeneity of the data. Limitations of this study include the participation rate; only 48.2% of the original cohort attended the 18-month health examination and the analysed subcohort represents 44.3% of the original cohort. It is likely that nonparticipating parents may have considered the health examination too much time-consuming as this comprehensive health check lasted for half a day. Nevertheless, we do not think that our participation rate could have caused major bias as the only differences between infants participating from those not participating were found in

maternal age and level of parental SES. Results from other birth cohort studies actually report that high SES parents are more willing to participate, probably because of an increased awareness of the disease (8). Moreover, it can be speculated that low SES parents might have less flexibility in their jobs to attend the health examination. No cost consideration should have influenced the participation rate as the health examination proposed in the follow-up of the cohort was entirely free.

Conclusion

In conclusion, this study improves the knowledge on the natural history of AR by shedding light on the associations between AR-like symptoms and predisposition to atopy in the one hand, and biological markers of atopy on the other hand, as soon as 18 months of life. Our results should be of particular interest to clinicians investigating nasal disorders in infants. Suspicion of AR should be reinforced in infants with parental history of AR or biological evidence of atopy, particularly blood eosinophilia and sensitization to inhalant allergens.

Acknowledgments

This survey is supported by the Social, Childhood and Health Direction (DASES) of the Paris Council. We thank the Paris Child Health Centre that received infants at 18 months of age for the health examination, as well as the Paris Council St Marcel Centre. We also thank the National French Health Insurance System Laboratory which performed cell blood counts and the Groupe Hospitalier Trousseau-La Roche Guyon, Biochemistry Laboratory, Assistance Publique – Hôpitaux de Paris, and especially Pr. Georges Morgant, for the measurements of total and allergen-specific IgE. We are grateful to the administrative staff, Chrystèle Grouas, Dominique Viguier and Leïla Blusseau, for their involvement in the PARIS cohort study and particularly for well-supervising appointments for the health examination at 18 months of age.

References

1. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;**63**(Suppl 86):8–160.
2. Arshad SH, Tariq SM, Matthews S, Hakim E. Sensitization to common allergens and its association with allergic disorders at age 4 years: a whole population birth cohort study. *Pediatrics* 2001;**108**:E33.
3. Ghunaim N, Wickman M, Almqvist C, Soderstrom L, Ahlstedt S, van Hage M. Sensitization to different pollens and allergic disease in 4-year-old Swedish children. *Clin Exp Allergy* 2006;**36**:722–727.
4. Sih T, Mion O. Allergic rhinitis in the child and associated comorbidities. *Pediatr Allergy Immunol* 2010;**21**:e107–e113.
5. Chawes BL, Kreiner-Moller E, Bisgaard H. Objective assessments of allergic and non-allergic rhinitis in young children. *Allergy* 2009;**64**:1547–1553.
6. Bousquet J, Vignola AM, Demoly P. Links between rhinitis and asthma. *Allergy* 2003;**58**:691–706.
7. Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson Children's Respiratory Study: 1980 to present. *J Allergy Clin Immunol* 2003;**111**: 661–675, quiz 676.
8. Clarisse B, Nikasinovic L, Poinsard R, Just J, Momas I. The Paris prospective birth cohort study: which design and who participates? *Eur J Epidemiol* 2007;**22**:203–210.
9. Just J, Nicoloyanis N, Chauvin M, Pribil C, Grimfeld A, Duru G. Lack of eosinophilia can predict remission in wheezy infants? *Clin Exp Allergy* 2008;**38**:767–773.
10. Poysa L, Remes K, Korppi M, Juntunen-Backman K. Atopy in children with and without a family history of atopy. I. Clinical manifestations, with special reference to diet in infancy. *Acta Paediatr Scand* 1989;**78**: 896–901.
11. Masuda S, Fujisawa T, Katsumata H, Atsuta J, Iguchi K. High prevalence and young onset of allergic rhinitis in children with bronchial asthma. *Pediatr Allergy Immunol* 2008;**19**:517–522.
12. Wright AL, Holberg CJ, Martinez FD, Halonen M, Morgan W, Taussig LM. Epidemiology of physician-diagnosed allergic rhinitis in childhood. *Pediatrics* 1994;**94** (6 Pt 1):895–901.
13. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;**332**:133–138.
14. Bohme M, Lannero E, Wickman M, Nordvall SL, Wahlgren CF. Atopic dermatitis and concomitant disease patterns in children up to two years of age. *Acta Derm Venereol* 2002;**82**:98–103.
15. Gillespie J, Wickens K, Siebers R, Howden-Chapman P, Town I, Epton M et al. Endotoxin exposure, wheezing, and rash in infancy in a New Zealand birth cohort. *J Allergy Clin Immunol* 2006;**118**:1265–1270.
16. Gehring U, Cyrys J, Sedlmeir G, Brunekreef B, Bellander T, Fischer P et al. Traffic-related air pollution and respiratory health during the first 2 yrs of life. *Eur Respir J* 2002;**19**:690–698.
17. Ballardini N, Nilsson C, Nilsson M, Lilja G. ImmunoCAP Phadiatop Infant – a new blood test for detecting IgE sensitisation in children at 2 years of age. *Allergy* 2006;**61**:337–343.
18. Tariq SM, Matthews SM, Hakim EA, Stevens M, Arshad SH, Hide DW. The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. *J Allergy Clin Immunol* 1998; **101**:587–593.
19. Arshad SH, Stevens M, Hide DW. The effect of genetic and environmental factors on the prevalence of allergic disorders at the age of two years. *Clin Exp Allergy* 1993;**23**:504–511.
20. Clarisse B, Demattei C, Nikasinovic L, Just J, Daures JP, Momas I. Bronchial obstructive phenotypes in the first year of life among Paris birth cohort infants. *Pediatr Allergy Immunol* 2009;**20**:126–133.
21. Marinho S, Simpson A, Lowe L, Kissen P, Murray C, Custovic A. Rhinoconjunctivitis in 5-year-old children: a population-based birth cohort study. *Allergy* 2007;**62**:385–393.
22. Wadonda-Kabondo N, Sterne JA, Golding J, Kennedy CT, Archer CB, Dunnill MG. Association of parental eczema, hayfever, and asthma with atopic dermatitis in infancy: birth cohort study. *Arch Dis Child* 2004;**89**:917–921.
23. Nickel R, Illi S, Lau S, Sommerfeld C, Bergmann R, Kamin W et al. Variability of total serum immunoglobulin E levels from birth to the age of 10 years. A prospective evaluation in a large birth cohort (German Multicenter Allergy Study). *Clin Exp Allergy* 2005;**35**:619–623.
24. Matricardi PM, Bockelbrink A, Gruber C, Keil T, Hamelmann E, Wahn U et al. Longitudinal trends of total and allergen-specific

IgE throughout childhood. *Allergy* 2009;**64**: 1093–1098.
25. Baldacci S, Omenaas E, Oryszczyn MP. Allergy markers in respiratory epidemiology. *Eur Respir J* 2001;**17**:773–790.
26. Kulig M, Bergmann R, Klettke U, Wahn V, Tacke U, Wahn U. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. *J Allergy Clin Immunol* 1999;**103**:1173–1179.
27. Kulig M, Klettke U, Wahn V, Forster J, Bauer CP, Wahn U. Development of seasonal allergic rhinitis during the first 7 years of life. *J Allergy Clin Immunol* 2000;**106**:832–839.
28. Wahn U, Bergmann RL, Nickel R. Early life markers of atopy and asthma. *Clin Exp Allergy* 1998;**28**(Suppl 1):20–21; discussion 32–6.
29. Perkin MR, Strachan DP, Hc W, Lack G, Golding J. The predictive value of early life total immunoglobulin E measurement in identifying atopic children in a population-based birth cohort study. *Pediatr Allergy Immunol* 2006;**17**:118–124.
30. Keil T, Kulig M, Simpson A, Custovic A, Wickman M, Kull I et al. European birth cohort studies on asthma and atopic diseases: II. Comparison of outcomes and exposures – a GA2LEN initiative. *Allergy* 2006;**61**:1104–1111.
31. Lowe AJ, Carlin JB, Bennett CM, Hosking CS, Abramson MJ, Hill DJ et al. Do boys do the atopic march while girls dawdle? *J Allergy Clin Immunol* 2008;**121**:1190–1195.
32. de Benedictis FM, Franceschini F, Hill D, Naspitz C, Simons FE, Wahn U et al. The allergic sensitization in infants with atopic eczema from different countries. *Allergy* 2009;**64**:295–303.
33. Kusel MM, de Klerk N, Holt PG, Sly PD. Antibiotic use in the first year of life and risk of atopic disease in early childhood. *Clin Exp Allergy* 2008;**38**:1921–1928.
34. Borres MP, Odelram H, Irander K, Kjellman NI, Bjorksten B. Peripheral blood eosinophilia in infants at 3 months of age is associated with subsequent development of atopic disease in early childhood. *J Allergy Clin Immunol* 1995;**95**:694–698.
35. Kajosaari M, Saarinen UM. Evaluation of laboratory tests in childhood allergy. Total serum IgE, blood eosinophilia and eosinophil and mast cells in nasal mucosa of 178 children aged 3 years. *Allergy* 1981;**36**:329–335.